Sunscreens Protect Epidermal Langerhans Cells and Thy-1+ Cells But Not Local Contact Sensitization from the Effects of Ultraviolet Light

Kenneth K.-L. Ho, Gary M. Halliday, and Ross St.C. Barnetson
Department of Dermatology, University of Sydney, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia

This study compares the ability of two commonly used sunscreens — octyl dimethyl para-aminobenzoate (Padimate O) and 2-ethylhexyl-p-methoxycinnamate (2-EHMC) — to protect Langerhans cells (LC), Thy-1+ dendritic epidermal cells (Thy-1+ dEC), and local contact sensitivity (CS) from the effects of ultraviolet (UV) light. Chronic exposure of mice 5 d per week for 4 weeks with an intermediate dose of solar-simulated sunlight from which any UVC had been filtered reduced the LC and Thy-1+ dEC density of murine epidermis. This irradiation procedure was designed to simulate closely the daily exposure of humans to sunlight. This effect on LC and Thy-1+ dEC occurred in both albino and pigmented mice that develop a tan during the irradiation procedure, indicating that a tan does not protect these cells from the effects of UV light. Sunscreen preparations with Padimate O and 2-EHMC, both of which also contained benzophenone-3, as well as Padimate O or 2-EHMC in organic solvent, inhibited UV light from depleting LC from the epidermis of both mouse strains. Padimate O and 2-EHMC in organic solvent were used to ensure that these were the active ingredients in the sunscreen preparations. In contrast to the effects on LC, Padimate O, but not 2-EHMC, protected Thy-1+ dEC from UV exposure in both mouse strains, but neither protected against the development of local immunosuppression using a contact sensitivity model. Thus, even in a mouse strain that is sensitive to UV-induced immunosuppression, local immunosuppression can occur in the presence of normal densities of LC and Thy-1+ dEC.
J Invest Dermatol 98:720–724, 1992

Ultraviolet light (UV), which is one of the prime causes of skin cancer in humans, also causes immunosuppression [1]. UV-induced immunosuppression has been proposed as an important mechanism by which highly immunogenic UV-induced neoplastic cells escape immune destruction [2]. Experimentally, UV-induced immunosuppression can be divided into local and systemic. Local immunosuppression is the reduced contact sensitivity (CS) response that occurs when contact sensitizers are applied locally to UV-irradiated skin. A reduced CS response also results from the application of contact sensitizer to a skin site distal to that which received the irradiation; this is referred to as systemic immunosuppression

Langerhans cells (LC) and Thy-1+ dendritic epidermal cells (Thy-1+ dEC) are constituents of the skin immune system. LC are epidermal antigen-presenting cells capable of initiating a specific T-lymphocyte–mediated immune response [3]. Thy-1+ dEC express CD3 and the γ/δ T-lymphocyte receptors for antigen [4,5] and hence are T cells; however, their function within the epidermis is unknown. Both LC and Thy-1+ dEC are depleted following UV exposure but, although the number of LC recovers following UV irradiation, the Thy-1+ cells remain depleted [6,7].

UV-induced depletion of local LC may be one of the events involved in the development of local immunosuppression [8,9]. Systemic UV-induced immunosuppression is not due to effects on LC as they are not disturbed at sites distant to those that received the irradiation [10]. Systemic immunosuppression is likely due to the production of soluble factors such as cis-urocanic acid [11], prostaglandins [12] and keratinocyte-derived factors [13].

Sunscreens are commonly used by humans to prevent sunlight-induced erythema, and there is some evidence in mice that they reduce the incidence of skin cancer [14]. However, there has not been a comparative study on the effects of the two most commonly used sunscreens, octyl dimethyl para-aminobenzoate (Padimate O) and 2-ethylhexyl-p-methoxycinnamate (2-EHMC), on LC, Thy-1+ dEC, and local contact sensitization. Hence, in this study we investigated the abilities of these two sunscreens to affect UV-induced LC and Thy-1+ dEC depletion as well as local immunosuppression. To determine whether pigmentation affects these parameters of the skin immune system, two mouse strains were compared, one albino (HRA : Skh-1), the other lightly pigmented and capable of developing a tan in response to UV irradiation (HRA : Skh-2).

MATERIALS AND METHODS

Animals Inbred HRA : Skh-1 hairless albino mice were bred and housed in the animal house of the Department of Veterinary Pathol-

Manuscript received April 3, 1991; accepted for publication September 30, 1991.

This project was supported by grants from the Leo and Jenny Leukaemia and Cancer Foundation of Australia, the University of Sydney, and the Clive and Vera Ramaciotti Foundations.

Reprint requests to: Dr. Gary Halliday, Department of Dermatology, University of Sydney, Gloucester House, Royal Prince Alfred Hospital, Missenden Road, Camperdown, N.S.W. 2050, Australia.

Abbreviations:
ANOVA: analysis of variance
CS: contact sensitivity
2-EHMC: 2-ethylhexyl-p-methoxycinnamate
LC: Langerhans cells
Padimate O: octyl dimethyl para-aminobenzoate
SPF: sun protection factor
Thy-1+ dEC: Thy-1+ dendritic epidermal cells
TNCB: 2,4,6-trinitrochlorobenzene
UV: ultraviolet light

0022-202X/92/$05.00

ogy, University of Sydney, Sydney, Australia. They originated from the Skin Cancer and Photobiology Unit, Temple University, Philadelphia, PA. HRA:Skh-2 are a new line of inbred mice established in the Department of Veterinary Pathology, University of Sydney. These are pigmented mice that also originated from the HRA:Skh-2 outbred stock from the Skin Cancer and Photobiology Unit, Temple University. This HRA:Skh-2 line became congeneic with HRA:Skh-1 mice after back crossing with HRA:Skh-1 mice for more than 20 generations [15].

Ultraviolet Irradiation Simulated solar UV radiation was provided by a bank of fluorescent tubes housed in a planar arrangement in a reflective batten. The fluorescent tubes consisted of six Sylvania F40BL UVA tubes flanking a single Oliphant FL40SE UVB tube. Emitted radiation was filtered through a layer of Kodacel (Eastman Chemical Products Inc., Kingsport, TN) cellulose acetate film (0.125 mm) that reduced radiation sharply below 295 nm, thus filtering out any UVC. The spectral properties of this light source have been described previously [14]; the integrated irradiance was 2.7×10^{-4} W/cm² for UVB (290–315 nm) and 5.2×10^{-3} W/cm² for UVA (315–400 nm).

Except for the contact sensitization experiments, the mice were irradiated while unrestricted in their cages with the minimal erythemal dose previously determined to be 10 min. Irradiation was applied 5 d per week for 4 weeks. Exposure times were increased every week by 20% of the initial exposure time to overcome acquired tolerance so that the minimal erythemal dose was maintained. Average cumulative doses were 4.2 J/cm² UVB and 81.1 J/cm² UVA.

Sunscreens Two sunscreen preparations were used. The Padimate O sunscreen preparation contained octyl dimethyl para-aminobenzoate (Padimate O) at 6.5% and benzophenone-3 at 3% in an unspecified base lotion (Sundown Sunscreen Lotion; Johnson & Johnson, Sydney, Australia). The Cinnamate sunscreen preparation contained 7.5% 2-ethylhexyl-p-methoxycinnamate (2-EHMC) and benzophenone-3 at 4.5% in an unspecified base lotion (Genescreen; Photobiological Research Inc., Cedar Crest, NM, USA). According to the manufacturers, both sunscreens have sun protection factors of 15.

Both pure Padimate O (ICI Australia, Sydney, Australia) or 2-EHMC (Givaudan Pty. Ltd., Sydney, Australia) were dissolved in a solvent consisting of ethanol, dimethylsulphoxide, and acetone (1:1:6; v/v/v) at the same concentration as in the sunscreen preparations described above, i.e., 6.5% Padimate O or 7.5% 2-EHMC.

Sunscreens were applied topically to the dorsal trunk of mice 10 min prior to commencement of irradiation or sham-irradiation 5 d per week for 4 weeks. The quantity of sunscreen used for each application was equivalent to 2 mg of pure sunscreen/cm².

Langerhans Cell and Thy-1+ Cell Quantification At the end of treatment, the mice were killed, the stratum corneum of the dorsal trunk skin removed by repeated applications of cellophane tape, and the treated dorsal trunk skin excised. The excised skin was adhered onto cellophane tape, incubated in 20 mM phosphate-buffered ethylenediamine tetraacetic acid solution (pH 7.3) and incubated at 37°C for 3 h. The epidermis was then separated from the dermis using a dissecting microscope and a pair of fine forceps, and the cellophane tape removed [16].

The epidermal sheets were then stained by an indirect immunoalkaline phosphatase technique to detect LC or Thy-1+ dEC as described previously [17]. Primary antibodies were hybridoma supernatants containing rat anti-Ia (TIB 120; [18]) or anti-Thy-1 (T24.31.7 [19]) monoclonal antibodies to stain LC and Thy-1+ cells respectively. The stained cells were enumerated manually with the assistance of an image analysis system attached to a light microscope (Chromatic Colour Image Analysis System, Leitz, Sydney, Australia). For each mouse, cells were counted within six separate randomly selected regions, incorporating a total area of 0.3 mm².

Contact Sensitization For the contact sensitization experiments, mice were restrained by mesh wire during irradiation so that their ears could be shielded from UV by tin foil. Mice were sensitized with 50 μl of 1% 2,4,6-trinitrochlorobenzene (TNCB) (Tokyo Kasei, Japan) in acetone/olive oil (4:1, v/v) topically applied twice to the dorsal trunk 24 h apart on days 0 and 1. Mice were then challenged on day 5 with 5 μl of 0.5% TNCB on each side of the right ear. Ear swelling was then assessed 24 h following challenge by measuring the increase in ear thickness with an engineer's micrometer (Mercer, St. Albans, England). The local contact sensitivity (CS) response was calculated using the formula

$$\frac{\text{right ear thickness} - \text{left ear thickness}}{\text{left ear thickness} \quad 1} \times 100.$$

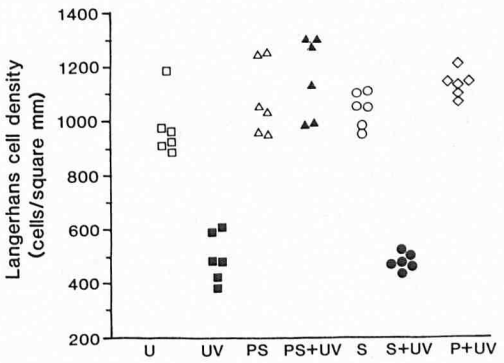

Figure 1. Effects of UV irradiation on LC densities in Padimate O–treated HRA:Skh-1 mice. U, untreated mice; UV, mice irradiated with UV light; PS, mice treated with the Padimate O based sunscreen preparation; PS + UV, mice treated with the Padimate O based sunscreen preparation and irradiated with UV light; S, mice treated with the solvent in which Padimate O was dissolved; S + UV, mice treated with the solvent in which Padimate O was dissolved and irradiated with ultraviolet light; P + UV, mice treated with Padimate O dissolved in solvent and irradiated with ultraviolet light. Each *point* represents an individual mouse.

Statistics For statistical analysis, the analysis of variance (ANOVA) for factorial models was used to analyze cell densities. Contact sensitivity results were not normally distributed, and hence were analyzed using the Mann-Whitney U test. A p value of < 0.01 was regarded as significant.

RESULTS

Langerhans Cell Densities

Albino Mice: LC were significantly depleted from treated epidermis after 4 weeks of daily UV irradiation compared to unirradiated mice ($p < 0.001$, ANOVA; F stat for equal means: 53.791 df 6.41) (Fig 1). Mice treated with either the Padimate O sunscreen preparation containing benzophenone-3 or Padimate O in solvent had LC densities that did not differ significantly from each other or from untreated mice. Irradiation of mice treated with Padimate O sunscreen preparation or Padimate O in solvent did not significantly reduce the LC density below any of the unirradiated groups. In contrast, irradiated mice pretreated with topical solvent had LC densities that did not differ from the group receiving UV only, and which were significantly ($p < 0.001$) lower than any of the groups treated with Padimate O.

The LC densities of mice irradiated through either the 2-EHMC sunscreen preparation containing benzophenone-3 or 2-EHMC in solvent were not significantly different (ANOVA; F stat for equal means: 70.251 df 6.41) from that found in the unirradiated control, but significantly higher than mice irradiated through untreated or solvent-treated skin ($p < 0.001$ for each group) (Fig 2). Thus, topical application of 2-EHMC prior to UV effectively prevented UV-induced depletion of LC.

Pigmented Mice: After 4 weeks of daily UV irradiation of 6 HRA:Skh-2 mice per group, the mean LC density dropped signifi-

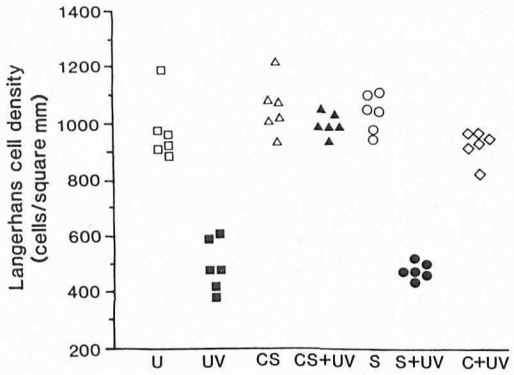

Figure 2. Effects of UV irradiation on LC densities in 2-EHMC treated HRA : Skh-1 mice. U, untreated mice; UV, mice irradiated with UV light; CS, mice treated with the 2-EHMC based sunscreen preparation; CS + UV, mice treated with the 2-EHMC based sunscreen preparation and irradiated with UV light; S, mice treated with the solvent in which 2-EHMC was dissolved; S + UV, mice treated with the solvent in which 2-EHMC was dissolved and irradiated with ultraviolet light; C + UV, mice treated with 2-EHMC dissolved in solvent and irradiated with ultraviolet light. Each *point* represents an individual mouse.

cantly from 980.5 (±121.9) cells per mm² for the unirradiated group to 368.9 (±54.1) cells per mm² for the mice treated with UV (ANOVA; F stat for equal means: 85.82 df 3.23). In contrast, irradiation of mice treated with the Padimate O sunscreen preparation did not significantly reduce the LC density; the mean density for the irradiated group was 892.8 (±58.6) cells per mm² whereas the unirradiated controls treated with Padimate O had an LC density of 960.8 (±48.6) cells per mm². HRA : Skh-2 mice treated with the 2-EHMC sunscreen preparation prior to irradiation had a mean LC density of 1180.1 (±105.7) cells per mm², which was significantly higher than the mean LC density for the mice receiving UV alone, but not significantly different from untreated, unirradiated mice or the group treated with 2-EHMC alone(ANOVA; F stat for equal means: 104.35 df 3.23).

Thy-1+ dEC

Albino Mice: Thy-1+ dEC were significantly depleted from the epidermis of HRA : Skh-1 mice after 4 weeks of daily UV irradiation (Fig 3) ($p < 0.001$, ANOVA; F stat for equal means: 69.967 df 6.41). Thy-1+ dEC densities of the irradiated mice treated with either Padimate O sunscreen preparation or Padimate O in solvent were not significantly different from the unirradiated groups that were either untreated or treated with solvent or the Padimate O sunscreen preparation. In contrast, they were significantly higher than the groups that were irradiated through untreated or solvent-

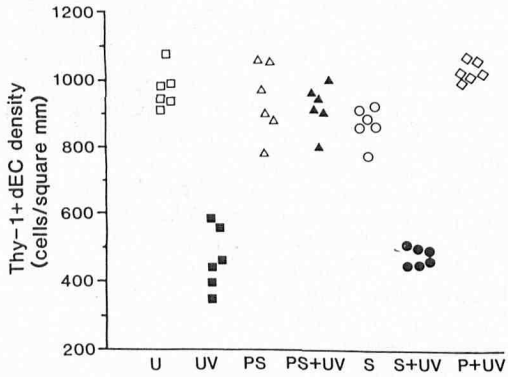

Figure 3. Effects of UV irradiation on Thy-1+ dEC densities in Padimate O treated HRA : Skh-1 mice. Rest of legend as for Fig 1.

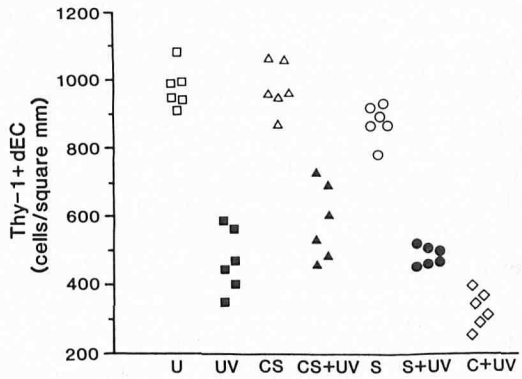

Figure 4. Effects of UV irradiation on Thy-1+ dEC densities in 2-EHMC treated HRA : Skh-1 mice. Rest of legend as for Fig 2.

treated skin ($p < 0.001$ for each group). Padimate O without irradiation did not significantly alter Thy-1+ dEC density. Thus, topical application of Padimate O prior to UV completely prevented UV-induced depletion of Thy-1+ dEC.

In contrast to the protective effects of 2-EHMC against UV-induced depletion of LC, 2-EHMC failed to prevent UV-induced Thy-1+ dEC depletion (Fig 4). Mice treated with either the 2-EHMC sunscreen preparation or 2-EHMC in solvent prior to UV irradiation had mean Thy-1+ dEC densities significantly lower than unirradiated mice or the group treated with 2-EHMC sunscreen preparation only ($p < 0.001$ in each case; ANOVA; F stat for equal means: 82.182 df 6.41). They were not significantly different from the untreated, irradiated mice. 2-EHMC alone did not significantly alter Thy-1+ dEC density.

Pigmented Mice: Thy-1+ dEC were significantly ($p < 0.001$; ANOVA; F stat for equal means: 14.76 df 3.23) depleted from the epidermis of HRA : Skh-2 mice from a mean of 958.8 cells per mm² (six mice per group) for the unirradiated group to 598.1 cells per mm² after 4 weeks of daily UV irradiation. Irradiated mice treated with the Padimate O sunscreen preparation had a mean Thy-1+ dEC density of 963.7 cells per mm², which was not significantly different from unirradiated mice treated with Padimate O (909.6 cells per mm²) or unirradiated, untreated mice, but was significantly higher than that of the group that received UV only.

Irradiation of HRA : Skh-2 mice that had been treated with 2-EHMC significantly decreased ($p < 0.001$; ANOVA; F stat for equal means: 28.47 df 3.23) the Thy-1+ dEC density from 1045.3 cells per mm² to 612.81 cells per mm². The mean Thy-1+ dEC density of the irradiated mice treated with 2-EHMC was not significantly different from irradiated mice without sunscreen treatment.

Contact Hypersensitivity HRA : Skh-1 mice were sensitized by the local application of TNCB onto the irradiated skin (Fig 5). The CS response of untreated unirradiated mice was significantly higher than that of the untreated irradiated mice ($p < 0.01$; Mann-Whitney U test). Treatment with either the Padimate O or 2-EHMC sunscreen preparation containing benzophenone-3 did not prevent UV irradiation from reducing the CS response because it was significantly lower in both of these groups than in the untreated unirradiated group ($p < 0.01$ for each group). Neither sunscreen significantly reduced the CS response in the absence of irradiation. The unirradiated mice that were not sensitized, but challenged only with TNCB, developed a 9.2% median increase in ear thickness, which indicated that the CS response required prior contact with antigen during the sensitization phase.

DISCUSSION

The HRA : Skh-1 and -2 mice are congeneic, Skh-1 being albino whereas Skh-2 possess melanocytes in the basal layer of the epidermis that are capable of producing melanin. Skh-2 mice are constitutively lightly pigmented except in their ears and tail where strong

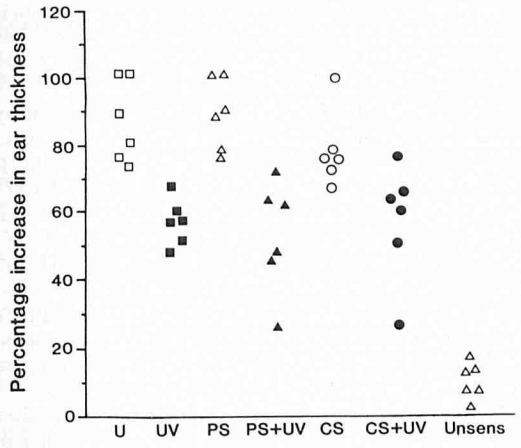

Figure 5. Effects of UV irradiation on contact sensitivity responses in Padimate O or 2-EHMC treated HRA:Skh-1 mice. U, untreated mice; UV, mice irradiated with UV light; PS, mice treated with the Padimate O based sunscreen preparation; PS + UV, mice treated with the Padimate O based sunscreen preparation and irradiated with UV light; CS, mice treated with the 2-EHMC based sunscreen preparation; CS + UV, mice treated with the 2-EHMC based sunscreen preparation and irradiated with UV light; Unsens, mice were untreated and not sensitized but ear challenged with TNCB only. Percentage increase in ear thickness used as a measure of the contact sensitivity response. Each *point* represents an individual mouse.

pigmentation occurs; however, they develop a tan when exposed to UV light. Therefore, compared with the albinos, the HRA:Skh-2 mice are probably more representative of Caucasian human skin and therefore were compared to albino mice in this study. We used an irradiation procedure designed to resemble intermediate dose chronic exposure of humans to sunlight. The solar-simulated UV light was filtered to remove any contaminating UVC and mice were exposed to the minimal erythemal dose 5 d per week for 4 weeks.

LC and Thy-1+ dEC were reduced to similar levels in both the albino and tanning mice, indicating that the development of a tan during UV irradiation does not protect these cells from the effects of UV light. This is in agreement with previous findings in humans that a tan does not protect LC from the effects of UV light [20].

Sunscreens are effective agents for the prevention of UV-induced erythema (sunburn). Both commercial sunscreens employed in our studies had sun protection factors (SPF) of 15 for humans, according to the manufacturers. When we applied these sunscreens to HRA:Skh-1 mice at 2 mg/cm^2, and exposed them to 15 times the minimal erythemal dose of UV light, a minimal erythemal response was not produced. Hence, the sunscreens gave an SPF factor of at least 15 in our mice. Sunscreens are also effective in preventing some pathologic changes associated with UV exposure, including epidermal sunburn cell formation and dermal damage [21]. Both Padimate O- and 2-EHMC-based sunscreens have been shown to reduce the incidence of UV-induced skin cancer in mice [14].

In this study we have demonstrated that both Padimate O- and 2-EHMC-based sunscreens, which also contained benzophenone-3, can protect LC from the effects of UV light. This protection occurred both in albino mice and in those that developed a tan in response to UV irradiation. Lynch et al [22] have previously shown that UV irradiation of mice treated with a commercial para-aminobenzoic acid-based sunscreen (5% w/w) reduced the density of ATPase+ epidermal cells 3 d following irradiation, but the LC returned to normal by day 7 of irradiation. Our data are consistent with these studies, that in the presence of sunscreens, LC numbers are normal after extended periods of UV irradiation. However, the functional capabilities of these LC are unknown. To our knowledge this is the first study to demonstrate that Padimate O- or 2-EHMC-based sunscreens also inhibit UV light from depleting the number of LC from the epidermis.

Whereas Padimate O was able to abolish the depletion of Thy-1+ dEC after UV, 2-EHMC failed to protect these cells. These results were found using both strains of mice and both a commercial sunscreen preparation and pure 2-EHMC or Padimate O in solvent, demonstrating that this is a difference between Padimate O and 2-EHMC rather than to other differences in the sunscreen preparations. There have been no previous reports on sunscreens and Thy-1+ dEC during UV irradiation. The reason for this dissimilarity between the sunscreens is unknown, but may be related to differences in absorption. In ethanol, Padimate O has a narrower absorption spectrum than 2-EHMC [23], absorbing less at lower (280-290 nm) and higher (330-350 nm) wavelengths. Both sunscreen preparations also contained benzophenone-3, which absorbs broadly in the UVA region, making it unlikely that differential absorption at higher wavelengths of UV accounts for the differences between these sunscreens. However, absorption by sunscreens is very solvent-dependent, and their spectrum in vivo is unknown. Hence, it is possible that the differences in absorption could be responsible for this dissimilarity between the sunscreens.

Despite the ability of both sunscreens to inhibit a depletion in LC numbers, although Padimate O (but not cinnamate) protected Thy-1+ dEC, neither sunscreen protected against the development of immunosuppression when a contact sensitizer was applied locally to irradiated skin. This is in agreement with previous reports that mice treated with para-aminobenzoic acid prior to UV still had a depressed contact hypersensitivity response when sensitized with 2,4-dinitro-1-fluorobenzene through the irradiated area [22].

Padimate O and para-aminobenzoic acid have been found not to protect against the development of systemic immunosuppression in mice to contact sensitizers [24,25], nor against the systemic immunosuppression that enables UV-induced tumor lines to grow when transplanted into the irradiated mice [24,26]. It has also been shown that Padimate O did not inhibit suppression of natural killer cell activity, systemic immunosuppression to a contact sensitizer, or depressed in vitro immunoglobulin production in response to pokeweed mitogen in humans [27]. In comparing Padimate O- and 2-EHMC-based sunscreens, Padimate O did not protect against systemic immunosuppression as determined by CS to 2,4-dinitrofluorobenzene and growth of a transplantable tumor line, whereas the 2-EHMC sunscreen did protect [23]. The same sunscreens and mouse strain were used in these experiments as in the present study; however, different radiation regimes were used. In the study by Reeve et al [23] the mice were irradiated for three consecutive days with a single UVB tube from which UVC was not filtered, and received a total of 0.354 J/cm^2 UVB. In contrast, our UV-irradiation source was filtered to remove UVC and a similar ratio of UVA:B as is present in sunlight was used for irradiation. In the present study the mice were irradiated 5 d per week for 4 weeks, receiving a total dose of 4.2 J/cm^2 UVB and 81.1 J/cm^2 UVA. Hence, the protection by 2-EHMC observed by Reeve et al and the lack of protection in our experiments may have been due to either the lower total dose of UV or the presence of UVC. 2-EHMC is a stronger absorber of UVC than Padimate O [23] and therefore may be a more efficient sunscreen when UVC is present. In contrast, in our experiments the immunosuppression is more likely to have been caused by UVB.

The reasons for the inability of sunscreens to protect against UV-induced immunosuppression despite their ability to protect against LC depletion remain unknown. The LC found in the irradiated epidermis pretreated with sunscreens may not be functional, or other local effects of UV light may not have been inhibited by the sunscreens. UV irradiation alters lymphocyte migration [28] and may influence LC migration to the local lymph nodes. Expression of adhesion molecules is also altered by UV light [29]; the effect of sunscreens on adhesion molecule expression has not been investigated. Alternatively, UV-induced factors responsible for systemic immunosuppression may still be produced in the presence of sunscreens and these may have been responsible for the local immunosuppression observed in this study as well as the systemic immunosuppression in the presence of sunscreens reported by others. Local immunosuppression may be due to both depletion of local LC as

well as systemic immunosuppressive factors. Noonan et al [10] have observed that 8200 J/m² of narrow band 320 nm UV can cause systemic suppression of CS without depleting LC, whereas 200 J/m² of 270 nm UV can deplete LC without affecting systemic CS. Thus, it is possible that the sunscreens absorb the wavelengths of UV responsible for reducing LC density, though allowing transmission of sufficient energy of the wavelengths responsible for systemic immunosuppression.

Thus, it appears that sunscreens do not offer complete biologic protection against the effects of sunlight, which is important considering the number of humans who expose themselves to sunlight for extended periods while using sunscreens. Furthermore, our studies indicate that UV-induced immunosuppression can occur in the presence of normal numbers of LC, suggesting either that other local effects of UV light are not inhibited by sunscreens, or that systemic immunosuppressive factors may also partly mediate local UV-induced immunosuppression, and that these factors may still be produced in the presence of sunscreens.

We wish to thank Dr. V. Reeve, Department of Veterinary Pathology, University of Sydney for the kind gift of the HRA : Skh-2 mice and for his helpful discussions.

REFERENCES

1. Morison WL: Effects of ultraviolet radiation on the immune system of humans. Photochem Photobiol 50:515–524, 1989
2. Fisher MS, Kripke ML: Systemic alteration induced in mice by ultraviolet light irradiation and its relationship to ultraviolet carcinogenesis. Proc Natl Acad Sci USA 74:1688–1692, 1977
3. Streilein JW, Grammar SF, Yoshikawa T, Demidem A, Bermeer M: Functional dichotomy between Langerhans cells that present antigen to naive and to memory/effector T lymphocytes. Immunol Rev 117:159–183, 1990
4. Kuziel WA, Takashima A, Bonyhadi M, et al: Regulation of T-cell receptor gamma-chain RNA expression in murine Thy-1+ dendritic epidermal cells. Nature 328:263–267, 1987
5. Stingl G, Koning F, Yamada H, et al: Thy-1+ dendritic cells express T3 antigen and the T-cell receptor γ chain. Proc Natl Acad Sci USA 84:5686–5690, 1987
6. Aberer W, Romani N, Elbe A, Stingl G: Effects of physicochemical agents on murine epidermal Langerhans cells and Thy-1–positive dendritic epidermal cells. J Immunol 136:1210–1216, 1986
7. Alcalay J, Craig JN, Kripke ML: Alteration in Langerhans cells and Thy-1+ dendritic epidermal cells in murine epidermis during the evolution of ultraviolet radiation-induced skin cancers. Cancer Res 49:4591–4596, 1989
8. Toews GB, Bergstresser PR, Streilein JW, Sullivan S: Epidermal Langerhans cell density determines whether contact hypersensitivity or unresponsiveness follows skin painting with DNFB. J Immunol 124:445–453, 1980
9. Cruz PD, Bergstresser PR: Ultraviolet radiation, Langerhans' cells, and skin cancer. Conspiracy and Failure. Arch Dermatol 125:975–981, 1989
10. Noonan FP, Bucana C, Sauder DN, De Fabo EC: Mechanism of systemic immune suppression by UV irradiation in vivo. J Immunol 132:2408–2416, 1984
11. Noonan FP, De Fabo EC, Morrison H: Cis-urocanic acid, a product formed by ultraviolet B irradiation of the skin, initiates an antigen presentation defect in splenic dendritic cells in vivo. J Invest Dermatol 90:92–99, 1988
12. Robertson B, Gahring L, Newton R, Daynes RA: In vivo administration of IL-1 to normal mice decreases their capacity to elicit contact hypersensitivity responses: prostaglandins are involved in this modification of the immune response. J Invest Dermatol 88:380–387, 1987
13. Kim T-Y, Kripke ML, Ullrich SE: Immunosuppression by factors released from UV-irradiated epidermal cells: selective effects on the generation of contact and delayed hypersensitivity after exposure to UVA or UVB radiation. J Invest Dermatol 94:26–32, 1990
14. Reeve VE, Greenoak GE, Gallagher CH, Canfield PJ, Wilkinson FJ: Effect of immunosuppressive agents and sunscreens on UV carcinogenesis in the hairless mouse. Aust J Exp Biol Med Sci 63:655–665, 1985
15. Reeve VE, Greenoak GE, Boehm-Wilcox C, Canfield PJ, Gallagher CH: Effect of topical 5-methoxypsoralen on tumorigenesis induced in albino and pigmented hairless mouse skin by UV irradiation. J Photochem Photobiol 5:343–357, 1990
16. Halliday GM, Odling KA, Ruby JC, Muller HK: Suppressor cell activation and enhanced skin allograft survival after tumor promotor but not initiator induced depletion of cutaneous Langerhans cells. J Invest Dermatol 90:293–297, 1988
17. Halliday GM, Reeve VE, Barnetson RStC: Langerhans cell migration into ultraviolet light-induced squamous skin tumors is unrelated to anti-tumor immunity. J Invest Dermatol 97:830–834, 1991
18. Bhattacharya A, Dorf ME, Springer TA: A shared alloantigenic determinant on Ia antigens encoded by the I-A and I-E subregions: evidence for I region gene duplication. J Immunol 127:2488–2495, 1981
19. Dennert F, Hyman R, Lesley J, Towbridge IS: Effects of cytotoxic monoclonal antibody specific for T200 glycoprotein on functional lymphoid cell populations. Cell Immunol 53:350–364, 1980
20. Scheibner A, Hollis DE, McCarthy WH, Milton GW: Effects of exposure to ultraviolet light in a commercial solarium on Langerhans cells and melanocytes in human skin. Aust J Dermatol 27:35–41, 1986
21. Kligman LH, Akin FJ, Kligman AM: Prevention of ultraviolet damage to the dermis of hairless mice by sunscreens. J Invest Dermatol 78:181–189, 1982
22. Lynch DH, Gurish MF, Daynes RA: Relationship between epidermal Langerhans cell density ATPase activity and the induction of contact hypersensitivity. J Immunol 126:1892–1897, 1981
23. Reeve VE, Bosnic M, Boehm-Wilcox C, Ley RD: Differential protection by two sunscreens from UV radiation-induced immunosuppression. J Invest Dermatol 97:624–628, 1991
24. Morison WL: The effect of a sunscreen containing Para-aminobenzoic acid on the systemic immunologic alterations induced in mice by exposure to UVB radiation. J Invest Dermatol 83:405–408, 1984
25. Fisher MS, Menter JM, Willis I: Ultraviolet radiation-induced suppression of contact hypersensitivity in relation to Padimate O and oxybenzone. J Invest Dermatol 92:337–341, 1989
26. Gurish MF, Roberts LK, Krueger GG, Daynes RA: The effects of various sunscreen agents on skin damage and the induction of tumor susceptibility in mice subjected to ultraviolet irradiation. J Invest Dermatol 76:246–251, 1981
27. Hersey P, MacDonald M, Burns C, Schibeci S, Matthews H, Wilkinson FJ: Analysis of the effects of a sunscreen agent on the suppression of natural killer cell activity induced in human subjects by radiation from solarium lamps. J Invest Dermatol 88:271–276, 1987
28. Spangrude GJ, Bernhard EJ, Ajioka RS, Daynes RA: Alterations in lymphocyte homing patterns within mice exposed to ultraviolet radiation. J Immunol 130:2974–2981, 1983
29. Norris DA, Lyons MB, Middleton MH, Yohn JJ, Kashihara-Sawami M: Ultraviolet radiation can either suppress or induce expression of intercellular adhesion molecule 1 (ICAM-1) on the surface of cultured human keratinocytes. J Invest Dermatol 95:132–138, 1990